

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 2003/103770 A3

(51) International Patent Classification⁷: **A61P 15/08**,
A61K 38/09, 38/24

(21) International Application Number:
PCT/NL2003/000370

(22) International Filing Date: 6 June 2003 (06.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02077221.6 7 June 2002 (07.06.2002) EP

(71) Applicant (for all designated States except US): **ARES
TRADING S.A.** [CH/CH]; Chateau de Vaumarcus,
CH-2028 Vaumarcus (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BUNSCHOTEN**,
Evert, Johannes [NL/NL]; Plantsoen 16, NL-5384 EV
Heesch (NL). **COELINGH BENNINK**, Herman, Jan,
Tijmen [NL/NL]; Melvill van Carnbeelaan 38, NL-3971
BE Driebergen (NL).

(74) Agent: **VAN WESTENBRUGGE**, Andries et al; Ned-
erlandsch Octrooibureau, Scheveningseweg 82, P.O. Box
29720, NL-2502 LS The Hague (NL).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
22 April 2004

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF CONTROLLED OVARIAN HYPERSTIMULATION AND PHARMACEUTICAL KIT FOR USE IN
SUCH METHOD

(57) Abstract: One aspect of the present invention is concerned with a method of controlled ovarian hyperstimulation in a mam-
malian female, said method comprising the co-administration to said female of - a substance having follicle stimulating hormone ac-
tivity (FSH substance) in an amount effective to stimulate multiple follicular development; - gonadotropin releasing hormone (GnRH)
antagonist in an amount equivalent to a daily subcutaneous dose of at least 0.5 mg ganirelix to prevent a premature LH-surge; and -
a LH substance in an amount effective to prevent or suppress symptoms of luteinising hormone (LH) deficiency resulting from the
administration of the GnRH antagonist; followed by administering a meiosis and luteinisation inducing substance (ML substance)
in an amount effective to stimulate resumption of meiosis and luteinisation, and wherein the LH substance is not obtained from the
urine of human females. Another aspect of the invention relates to a pharmaceutical kit for use in a method of controlled hyper-
stimulation, which kit comprises: - at least one parenteral or oral dosage unit containing one or more FSH substances in an amount
equivalent to a subcutaneous dose of 50-1500 I.U. FSH; -at least one parenteral dosage unit containing one or more GnRH antago-
nists in an amount equivalent to a subcutaneous dose of 0.5-25 mg ganirelix; -at least one parenteral dosage unit containing one or
more LH substances in an amount equivalent to a subcutaneous dose of 50-3000 I.U. recombinant LH; wherein the LH substance is
not obtained from the urine of human females.



WO 2003/103770 A3

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/NL 03/00370

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P15/08 A61K38/09 A61K38/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LUDWIG M ET AL: "Developments in drugs for ovarian stimulation." BEST PRACTICE & RESEARCH. CLINICAL OBSTETRICS & GYNAECOLOGY. APR 2003, vol. 17, no. 2, April 2003 (2003-04), pages 231-247, XP0009020046 ISSN: 1521-6934 the whole document ----- -/--	1-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 February 2004

Date of mailing of the international search report

02/03/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Skjöldebrand, C

INTERNATIONAL SEARCH REPORT

International Application No
100/NL 03/00370

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LISI FRANCO ET AL: "Use of recombinant follicle-stimulating hormone (Gonal F) and recombinant luteinizing hormone (Luveris) for multiple follicular stimulation in patients with a suboptimal response to in vitro fertilization." FERTILITY AND STERILITY, vol. 79, no. 4, April 2003 (2003-04), pages 1037-1038, XP0001179215 & ISSN: 0015-0282 abstract	1-15
P,X	----- BELAISCH-ALLART J ET AL: "Recommendations of good practice: Medicines that induce ovulation (June 2003)" GYNECOLOGIE OBSTETRIQUE FERTILITE 2003 FRANCE, vol. 31, no. 7-8, 2003, pages 676-686, XP0001155766 ISSN: 1297-9589 tables	1-15
P,X	----- HUGUES J-N ET AL: "LES PROTOCOLES DE STIMULATION OVARIENNE EN VUE DE FECONDATION IN VITRO: EVOLUTION AU COURS DES DERNIERES ANNEES. QU'EN EST-IL EN 2003? EVOLUTION OF PROTOCOLS FOR OVARIAN STIMULATION IN VITRO FERTILIZATION IN THE PAST YEARS: WHAT'S IN STORE IN 2003?" MTE. MEDECINE THERAPEUTIQUE ENDOCRINOLOGIE, JOHN LIBBEY EUROTEXT, MONTROUGE, FR, vol. 5, no. 1, 2003, pages 7-17, XP001155774 ISSN: 1295-9359 the whole document	1-15
P,X	----- JUST A ET AL: "Ovarian stimulation and ovulation induction is assisted reproduction" JOURNAL FUR FERTILITAT UND REPRODUKTION 2002 AUSTRIA, vol. 12, no. 4, 2002, pages 20-24, XP0009020112 ISSN: 1019-066X figures table 1	1-15
P,X	----- LUDWIG M ET AL: "Modern aspects of reproduction medicine" GYNAKOLOGE 2002 GERMANY, vol. 35, no. 9, 2002, pages 861-866, XP0001155767 ISSN: 0017-5994 the whole document	1-15
	----- -/--	

INTERNATIONAL SEARCH REPORT

International Application No
 RU/NL 03/00370

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/55357 A (ASTA MEDICA AG) 4 November 1999 (1999-11-04) the whole document	1-15
X	WO 98/58657 A (ORLEMANS EVERARDUS OTTO MARIA ; AKZO NOBEL NV (NL); COELINGH BENNINK H) 30 December 1998 (1998-12-30) cited in the application abstract page 4, paragraph 3	1-15
X	WO 01/000227 A (ORLEMANS EVERARDUS OTTO MARIA ; AKZO NOBEL NV (NL); VOORTMAN GERRIT (N) 4 January 2001 (2001-01-04) cited in the application the whole document	1-15
X	CN 1 199 642 A (ASTA MEDICA AG) 25 November 1998 (1998-11-25) cited in the application abstract	1-15
X	EP 0 788 799 A (ASTA MEDICA AG) 13 August 1997 (1997-08-13) the whole document	1-15
X	WIKLAND M ET AL: "A prospective, randomized comparison of two starting doses of recombinant FSH in combination with cetrorelix in women undergoing ovarian stimulation for IVF/ICSI" HUMAN REPRODUCTION (OXFORD), vol. 16, no. 8, August 2001 (2001-08), pages 1676-1681, XP0009020114 & ISSN: 0268-1161 abstract	1-15
X	RON-EL R ET AL: "INDUCTION OF OVULATION AFTER GNRH ANTAGONISTS" HUMAN REPRODUCTION UPDATE, OXFORD UNIVERSITY PRESS, OXFORD, GB, vol. 6, no. 4, July 2000 (2000-07), pages 318-321, XP001119287 the whole document	1-15
	-/--	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 03/00370

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FAUSER B C ET AL: "ENDOCRINE PROFILES AFTER TRIGGERING OF FINAL OOCYTE MATURATION WITH GNRH AGONIST AFTER COTREATMENT WITH TH GNRH ANTAGONIST GANIRELIX DURING OVARIAN HYPERSTIMULATION FOR IN VITRO FERTILIZATION" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, NEW YORK, NY, US, vol. 87, no. 2, February 2002 (2002-02), pages 709-715, XP008022669 ISSN: 0021-972X abstract	1-15
A	AL-INANY HESHAM ET AL: "GnRH antagonist in assisted reproduction: A Cochrane review" HUMAN REPRODUCTION (OXFORD), vol. 17, no. 4, April 2002 (2002-04), pages 874-885, XP0009020113 & ISSN: 0268-1161 the whole document	1-15
A	KRUSCHE C A ET AL: "The progesterone antagonist onapristone retards the advanced endometrial transformation after gonadotropin stimulation in rabbits" STEROIDS, BUTTERWORTH-HEINEMANN, STONEHAM, MA, US, vol. 65, no. 10-11, October 2000 (2000-10), pages 773-782, XP004224005 ISSN: 0039-128X abstract	1-15
A	BURGUES S ET AL: "THE EFFECTIVENESS AND SAFETY OF RECOMBINANT HUMAN LH TO SUPPORT FOLLICULAR DEVELOPMENT INDUCED BY RECOMBINANT HUMAN FSH IN WHO GROUP I ANOVULATION: EVIDENCE FROM A MULTICENTRE STUDY IN SPAIN" HUMAN REPRODUCTION, IRL PRESS, OXFORD, GB, vol. 16, no. 12, 2001, pages 2525-2532, XP001057228 ISSN: 0268-1161 the whole document	1-15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-15. relate to a compounds defined by reference to a desirable characteristic or property, namely

- 1) "a substance having follicle stimulating hormone activity"
- 2) "a GnRH antagonist"
- 3 "a LH-substance"
- 4) "a meiosis and luteinisation inducing substance"

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds disclosed in the examples
recFSH, cetrorelix, recLH and urinary hCG.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL 03/00370

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 03/00370

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9955357	A	04-11-1999	AT 252910 T AU 752415 B2 AU 3702899 A BR 9909802 A CA 2330131 A1 CZ 20003766 A3 DE 69912422 D1 DK 1082129 T3 WO 9955357 A1 EP 1082129 A1 HU 0101528 A2 JP 2002512975 T NO 20005145 A NZ 507405 A PL 343609 A1 SK 15302000 A3 TR 200003063 T2 US 6319192 B1	15-11-2003 19-09-2002 16-11-1999 26-12-2000 04-11-1999 15-08-2001 04-12-2003 26-01-2004 04-11-1999 14-03-2001 28-11-2001 08-05-2002 13-10-2000 25-10-2002 27-08-2001 08-10-2001 21-02-2001 20-11-2001
WO 9858657	A	30-12-1998	AU 8727798 A WO 9858657 A1 EP 0994718 A1 US 6653286 B1	04-01-1999 30-12-1998 26-04-2000 25-11-2003
WO 0100227	A	04-01-2001	AU 6263800 A CA 2341974 A1 WO 0100227 A1 EP 1140132 A1 JP 2003503358 T US 2003092628 A1	31-01-2001 04-01-2001 04-01-2001 10-10-2001 28-01-2003 15-05-2003
CN 1199642	A	25-11-1998	NONE	
EP 0788799	A	13-08-1997	EP 0788799 A2 JP 9227404 A	13-08-1997 02-09-1997